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A Case Series Providing Clinical Evidence that Methylone Produces Rapid and Robust Improvements in Major Depressive Disorder

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Abstract

Background: Methylone (3,4-methylenedioxy-N-methylcathinone; also known as MDMC, βk-MDMA, and M1), is a Rapid-Acting Entactogen (RAE) and phenethylamine compound with chemical and pharmacological properties similar to 3,4-Methylenedioxymethamphetamine (MDMA). A study comparing the acute effects of methylone and MDMA in healthy participants reported that while the subjective pharmacological effects of the two drugs were categorically similar, methylone demonstrated significant clinical, physiological, and pharmacological differences, including "softer" empathogenic and psychostimulant effects that may have potential for accelerated adoption across a broad range of medical settings and clinical applications. A recently published case series reported on methylone's potential as a treatment for stress- and trauma-related concerns, describing outcomes from 21 complex patients with PTSD as a primary diagnosis.

Objective: Here, we present a case series of clinical data from 7 patients (4 female, mean age = 42 years) treated with oral methylone for MDD in a naturalistic setting.

Methods: Archival data were used to examine patient characteristics and outcomes.

Results: Methylone was well tolerated. All patients achieved "very much improved" (n=3) or "much improved" (n=3) ratings on the Clinician Global Impressions-Improvement (CGI-I) scale.

Conclusion: Methylone appears to produce rapid, robust, and durable clinical benefits. There is an urgent need for rapid-acting, and robust interventions for MDD, especially for those patients not gaining clinical benefit from available treatments, such as SSRIs, and that can address some of the limitations and barriers to other rapid-acting interventions. These promising findings warrant further study to characterize the role and safety of methylone as a potential pharmacotherapy for MDD and other stress-related concerns.

Keywords: Major depressive disorder; Methylone; Treatment; Case series; Rapid Acting Entactogen

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Introduction

Depression is a common and often chronic psychiatric condition that is a leading cause of disability worldwide and a significant contributor to the global burden of disease [1]. Approximately 280 million people worldwide struggle with depression at any given time [1] and an estimated one in five US adults meet the criteria for Major Depressive Disorder (MDD) during their lifetime [2]. Despite substantial advances in treatment and symptom management strategies for MDD

over the past 25 years, the US prevalence of both adolescent and adult depression indicators has increased [3,4], and this disturbing trend appears similar on the global scale [1]. Further, though depression has more expansive first-line pharmacotherapy options than many other stress- and trauma-related disorders, up to 70% of people will continue experiencing burdensome symptoms despite receiving evidence-based antidepressant treatment [5-8], and less than 50% of patients respond to first-line antidepressant treatment or psychotherapy [9,10]. MDD that is treatment refractory, mostly described as Treatment-Resistant Depression (TRD), is characterized by marked significant functional impairment, a large burden on patients and their families, and is associated with great direct and indirect healthcare costs [11,12].

Many individuals with MDD who are treated with monoamine-based antidepressants – often a Selective Serotonin Reuptake Inhibitor (SSRI) – do not achieve full symptomatic and functional recovery with the index/first treatment [5-10,13]. SSRIs are Slow-Acting Antidepressants (SAADs) meaning they have a delayed onset of action requiring weeks to months continuous treatment for clinical benefit [14-16]. This latency period is troubling, as it increases risk for suicide and self-harm as well as other potentially destructive behaviors [17,18]. Not only do many people not benefit significantly from traditionally available pharmacotherapy options, but each time an individual is failed a treatment, their chances for a successful subsequent intervention experience decline. A study evaluating the trajectory of depression treatment and response to repeated attempts at pharmacologic treatments found remission rates of 36.8%, 30.6%, 13.7%, and 13.0% for the first, second, third, and fourth acute treatment steps, respectively [7]. Those that required more treatment steps demonstrated higher relapse rates as well, even when benefit was eventually noted [7]. Overall, remission rates are less than 15% among patients with two prior conventional treatment or augmentation failures (i.e., TRD) [19-23]. Furthermore, these traditionally available monoaminergic medications often lead to poor compliance [24] due to the delayed onset of action and adverse side effects [25-27] and many who are classified as 'treatment-responders' remain symptomatic and continue to lead restricted lives.

Given the limitations to traditionally available pharmacologic interventions, some prefer to attempt symptom management through psychotherapy [28]. Psychotherapy shows some efficacy in the treatment of depression; however, access to appropriately trained therapists is limited and the interventions can be challenging for patients. Further, despite the efficacy of manual-based psychotherapy (e.g., cognitive-behavioral therapy) in major depression, its efficacy as a monotherapy in TRD is not well established [29]. Efficacy of psychotherapy also can vary across the lifespan [30]. Regardless of treatment modality, troubling symptoms often persist even in patients classified as responders.

The past two decades have seen a paradigm shift in approaches to treating depression and have ushered in some novel Rapid-Acting Antidepressants (RAADs) including ketamine and mounting/renewed interest in psychedelic medicines. The serendipitous discovery of ketamine's RAAD effects began an avalanche of research into novel interventions and a focus on drugs that provide more rapid effects such as dissociative, hallucinogenic, and empathogenic experiences. Ketamine has been demonstrated to produce very rapid onset improvements in many patients, especially those with TRD [17,31]. In March 2019, intranasal esketamine (brand name Spravato) – the S enantiomer of ketamine – when co-administered with a conventional antidepressant, was approved by the U.S. Food and Drug Administration (FDA) for adults with TRD [32]. The European Medicines Agency granted regulatory approval for intranasal esketamine for TRD in December 2019. In August 2020, the FDA updated the approval of intranasal esketamine to include adults with major depression and suicidal ideation and behavior [33]. The addition of esketamine (and ketamine in an off-label format) to our pharmacological toolbox has been revolutionary in many ways and yet also is plagued with many limitations, most notably the required maintenance dosing for many patients to have a durable effect, intensive treatment schedule, and the high cost, limited insurance coverage and related restricted equitable access to the intervention [34,35].

The classic psychedelic medicine psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), a plant alkaloid and 5-HT2A receptor agonist found in the *Psilocybe* genus of mushrooms, has received much research, media, and public policy attention as a potential treatment for both MDD and TRD as well as other stress- and trauma-related concerns including substance use disorders, obsessive-compulsive disorder, and end-of-life anxiety, with future studies focused on PTSD. The US FDA granted a 'Breakthrough Therapy Designation' for specific synthetic psilocybin products for TRD (Compass Pathways) [36] and MDD (Usona) [37] in 2018 and 2019 respectively.

Recently, controlled trials have also demonstrated acute and enduring therapeutic effects in patients with PTSD – a psychiatric condition highly comorbid with MDD/TRD, after administration of two to three doses of 3,4-Methylenedioxymethamphetamine (MDMA) with manualized psychotherapy [38-41]. These robust enduring clinical effects were recently replicated in a large Phase 3 trial [42]. MDMA (product by the Multidisciplinary Association for Psychedelic Studies [MAPS]) was granted an FDA Breakthrough Therapy Designation, for PTSD specifically in 2017 [43].

Similar to ketamine, psilocybin- and MDMA assisted-therapies (medicine administration in conjunction with intensive psychotherapy, including preparation, dosing, and integration support) represent a potential paradigm shift in our approach to mental health care. However, though incredibly promising in many ways, these products are recognized to have limitations and challenges. Similarly – and perhaps even more concerning than with ketamine/esketamine - is the intensity of the interventions (hence, demands on patients' time), the required infrastructure (space, medical and mental health personnel time required during sessions for safety monitoring and support, therapist/facilitator training, etc.), and the significant cost will likely be barriers to equitable access and scalability.

Early evidence suggests methylone (3,4-methylenedioxy-N-methylcathinone; also known as MDMC, βk-MDMA, and M1), a Rapid Acting Entactogen (RAE) with a chemical structure similar to MDMA, holds potential to address the barriers and limitations noted in both SAADs (e.g., SSRIs) and other RAADs (e.g., ketamine, psilocybin, MDMA) while providing significant and durable clinical benefit. A recent study compared the acute pharmacological and physiological effects of orally administered methylone and MDMA in healthy participants with a history of recreational drug use. While they are structurally similar, methylone produced less intense psychostimulant and empathogenic effects relative to MDMA, including reduced physiological/cardiovascular effects (specifically

blood pressure, heart rate, and corporal temperature), euphoria, inebriation, and changes in cognitive and body perception, with increased pleasure and sociability [44]. It is suspected the milder pharmacological effects could be explained, in part, by differences in serotonin (5-HT) receptor affinity [45-48]. In addition to these differential clinical effects, preclinical data from a mouse model that is currently being prepared for publication suggests methylone administration produces a robust, fast-acting, antidepressant-like response in a standard Forced Swim Test (FST) that is greater in magnitude than fluoxetine or any other published data in the FST model including other SSRIs, TCAs, or other RAADs including ketamine [49].

A recently published case series of 21 diagnostically complex patients with a primary diagnosis of PTSD reported rapid-acting, robust, and durable improvements in symptoms following one or more doses of oral methylone [50]. The medicine appeared safe and was well tolerated with only four adverse events reported in total, none of which required intervention and all of which resolved quickly [50]. Notably, some PTSD patients in the report also were either taking concomitant SSRIs or had received a SSRI in the recent past and experienced clinical benefit with no adverse effects, which is notable as the trials of MDMA have required individuals stop these medications. This has important implications for patient care as tapering off SSRIs can be quite challenging and potentially dangerous. Preclinical studies suggest methylone is less serotonergic, with lower affinity for SERT and 13 times less potent inhibition of VMAT2 than MDMA [45,51]. Taken together this suggests that there is less serotonin depletion, less potential for neurotoxicity, and a high potential that methylone can be safely administered concurrently with SSRIs. Data being prepared for publication supports this assertion, as a rodent FST study showed pretreatment with SSRIs did not interfere with or influence the efficacy of methylone administration in producing an antidepressant effect [49].

Here we present a case series of seven patients with a primary diagnosis of MDD who received methylone treatment in a specialized outpatient setting. This provides the first clinical evidence to our knowledge of methylone's potential as a treatment for this population.

Case Presentation

Methods

Archival clinical data were obtained from seven (7) patients with a primary diagnosis of MDD who received one or more oral methylone administrations as part of specialty care in an outpatient psychiatric setting. This retrospective case series was reviewed and determined exempt from IRB approval by WCG IRB. No protected health information was disclosed and no consent was obtained from patients for the use of their data. Data was systematically compiled from information collected as part of routine clinical practice. Diagnoses were confirmed by an experienced clinician using semi-structured interviews. Baseline symptom severity and symptom improvement were evaluated using the Clinical Global Impressions Scale-Severity (CGI-S) [52] and Clinical Global Impressions Scale-Improvement (CGI-I) [52] respectively. Patients were evaluated for both observed and reported safety events following dosing sessions.

Results

Patient characteristics and clinical data are presented in Table 1. Of the 7 patients, four were female; all were Caucasian, with a mean age of 42 years (range: 22 to 76). Baseline CGI-S scores ranged between 4 and 6 (i.e., moderately to severely ill; see Figure 1). Prior or current therapies included: SSRIs/SNRIs (n=2), other psychoactive medications including lithium, methylphenidate, and an unspecified anticonvulsant (n=1), psychotherapy (n=7; 100%) including behavioral and cognitive therapy (n=1), humanistic methods (n=1), unspecified group (n=2) and individual therapy (n=2), inpatient therapy (n=1), unspecified experimental therapy (n=1), and somatic therapy (n=1). Two (28.6%) of these patients meet the commonly used standard definition for TRD, having not responded to two or more adequate antidepressant trials. All patients exhibited refractory disease, based on the more inclusive definition that includes both pharmacotherapy and psychotherapy trials as they have been engaged in multiple treatment modalities prior to methylone treatment and maintain a high level of symptom severity and impairment.

Dosing summary

Methylone was administered orally and concomitant medications were not changed, halted, or tapered with the exception of the one patient (case 3) who was "weaned off" lithium prior to dosing. In all cases, an additional "booster" dose of methylone was administered ~1 h after the initial dose to extend the therapeutic window and optimize clinical response. Starting doses were between 100 and 150 mg and total dosages in a given session, including boosters, ranged from 250 mg to 370 mg. All methylone doses were selected based on clinical judgment (provider has significant expertise with methylone administration and related therapy).

Clinical efficacy

All patients achieved significant improvement (CGI-I 1 "very much improved" or 2 "much improved") following treatment (Figure 1). This trend was observed even for those patients who received only a single session of methylone (n=2). For these two patients, both were reported to have made significant improvements after that session. For patients undergoing multiple methylone dosing sessions (n=5), initial improvement was noted after the first session in 80% (n=4) of patients. In addition to general symptom improvement demonstrated on the CGI-I, multiple patients reported improvements in notable specific presenting concerns throughout the course of methylone treatment including: Grief, anger, anhedonia, 'emotional unavailability,' aggression, suicidal ideation, and problematic alcohol use.

Case example

To further emphasize the magnitude of clinical effectiveness, we highlight the case of a 48-year-old female (case 1) with a complex and chronic history of MDD (over 20 years) with comorbid PTSD, suicidal ideation, borderline personality disorder, and alcohol dependence who had engaged in a myriad of treatments prior to methylone including multiple trials of SSRIs, multiple rounds of cognitive-behavioral and family systems psychotherapy, holotrophic breathwork, and body work/somatic treatment without any significant clinical benefit. After 3 months of treatment with methylone (6 sessions administered on a bi-monthly basis), the patient noted significant improvements across all symptoms (including reduced problematic alcohol use), as well as remission of anhedonia, depressed states, and suicidality. Clinical notes indicated, "Typical symptoms of PTSD and depression progressively dissolved, self-care improved, there was an "impressive emergence of artistic talent and expression (painting)," a new and fulfilling relationship with a romantic partner and noted a dramatic improvement in their relationship with her children."

Table 1: Demographics data, clinical characteristics, and response to treatment.

Case	Age (years)/ Sex (M/F)	Race/Ethnicity	Comorbidities	Prior Treatments	Total Methylone Dose Range Across all Sessions (mg) *including booster doses	#Observed Dosing Sessions	Treatment Duration	Baseline CGI-S	CGI-I
1	48/F	Caucasian	PTSD; borderline personality; alcohol abuse; eating disorder; obesity; SI	SSRI; behavioral and cognitive therapy; holotrophic breathwork; experimental therapy	250	"Numerous"	5 years	6	1
2	26/F	Caucasian	TRD	psychotherapy	360-370	3	6 months	4	2
3	22/M	Caucasian	Alcohol abuse; nicotine abuse; SI; handicap due to asphyxiation at birth; muscle spasm; leg paralysis, slurred speech; impaired sleep	lithium (tapered prior to methylone); anticonvulsant; methylphenidate; therapy	180	1	continued in group after 1st session	6	2*
4	22/M	Caucasian	N/A	therapy	250	1	continued in group after 1st session	5	2*
5	52/M	Caucasian	N/A	counseling; group therapy; humanisitc methods	250	4	9 months	5	1**
6	48/F	Caucasian	N/A	SSRI; inpatient therapy, group therapy; somatic therapy	250	4	9 months	6	1**
7	76/F	Caucasian	N/A	psychotherapy	246	2	1+ year	6	2

Notes: CGI-S: Clinical Global Impressions - Severity; CGI-I: Clinical Global Impressions - Improvement; N/A: Not Applicable; PTSD: Posttraumatic Stress Disorder; SI: Suicidal Ideation; TRD: Treatment-Resistant Depression; SSRI: Selective Serotonin Reuptake Inhibitor

*Case report data suggests patients "maintained improvement over years" though durability of the first session is unknown as they attended group methylone sessions every month or every other month for an unknown duration

**Patients no longer met diagnostic criteria for MDD following treatment

Durability

Information on durability of clinical effects was captured for six patients. One individual reported limited durability of significant improvement for about two weeks before a gradual return to baseline in between sessions; one reported sustained improvement approximately "80% of the time" with a duration of "at least two years" following three months of treatment, noting there were occasional (though significantly improved) experiences of depression or increased alcohol use; two maintained improvement "over years;" however, it is important to note that these individuals engaged in monthly or every-other-monthly group methylone sessions for an unknown duration. Of note, two patients (cases 5 and 6) no longer met criteria for MDD following their last session, one followed for two years and one for five years. Case 6 was a 48-year-old female patient with severe TRD that included inpatient hospitalizations as well as past treatments including SSRIs, multiple non-pharmacologic interventions such as group psychotherapy and somatic therapy. She no longer met criteria for MDD at the end of methylone treatment (4 dosing sessions) and maintained this benefit for at least two years.

Safety

Methylone was well tolerated, and no patients discontinued treatment due to adverse events. In fact, no patients were reported to have experienced any adverse effects. Some patients underwent "bi-annual extensive-data blood testing, to determine overall health, neurotransmitter balance, liver and kidney function, blood corpuscular data, hormone balance, etc. All parameters were unremarkable, and there were no observable negative effects that could be traced to the methylone treatment. One patient (case 7), a 76-year-old female, reported having previously taken MDMA in a clinical setting and found it had "too much thrust," and was "too harsh coming on," noting the effects were "too strong and brought on anxiety." She reported that methylone was "easier," "gentler," helped her to build a bond with her therapist, and after three sessions let her "feel like my old self, before I had so much grief." She also described that her sense of hopelessness was "gone."

Discussion

In this case series of patients with MDD, methylone administration produced acute and enduring improvements in MDD symptoms as measured by the CGI-I. The majority (86%) had baseline CGI-S of 5 or worse ("markedly" or "severely" ill). While the definition of refractory symptoms or TRD is subject to significant debate due to the heterogeneity of the condition and diversity in the constellation of symptoms and presenting concerns as well as a lack of specific and validated biomarkers, it is loosely defined as failure of two or more adequate therapeutic trials to provide at least moderate symptom relief [53-55]. More recently it has been suggested the inclusion of psychotherapy trials should also be considered in decisions about refractory symptoms. While only two of the patients in this case series have a documented history of SSRI trials that failed to produce clinical benefit, all patients have engaged in multiple trials of evidence-based interventions that did not result in significant clinical improvement prior to methylone treatment and can be considered treatment-

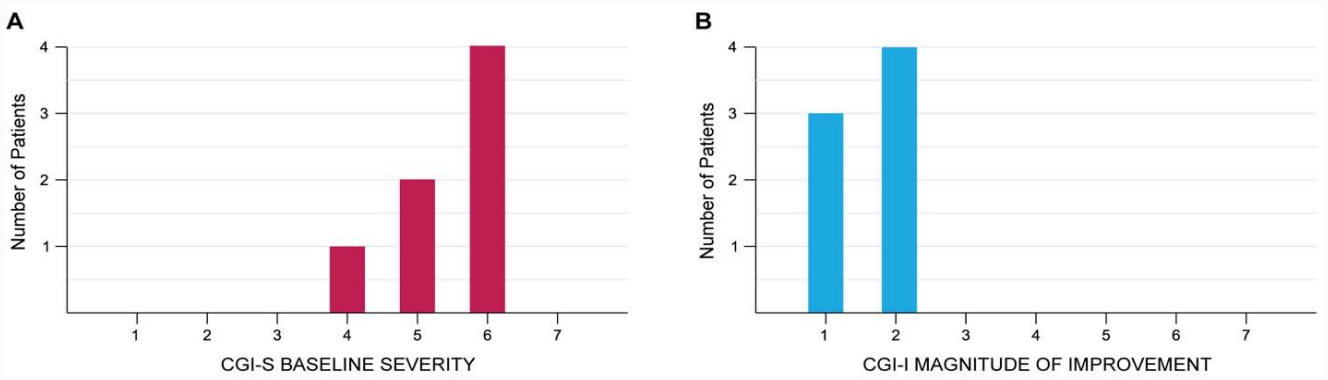

Figure 1: Baseline symptom severity and magnitude of improvement following methylone dosing.
Abbreviations: CGI-S: Clinical Global Impressions - Severity, where the higher the score the greater the severity of symptoms/impairment; CGI-I: Clinical Global Impressions - Improvement, where the lower the score the greater the magnitude of improvement

resistant. All patients achieved scores per CGI-I corresponding to "much improved" or "very much improved." Methylone was well-tolerated over a broad dose range and a varied number of sessions with no adverse effects being noted, even among this patient group with complex and chronic histories. The preliminary results summarized for this case series warrants further investigation of methylone as a potential treatment for MDD and add to the recently published case series in patients with PTSD [50]. Together these reports provide support for continued investigation, particularly in complex patients and those on concurrent SSRIs, as these experiences suggest that methylone was safe and well-tolerated, showed rapid and robust clinical efficacy, and generally durable effects in a population that would generally have been excluded from traditional controlled drug trials.

These rapid and robust antidepressant effects demonstrated following methylone administration are similar to those reported in ketamine trials, with the added benefit of extended durability of clinical benefit secondary to methylone treatment (relative to the generally brief [7-14 day with a single ketamine dose]; durability can be extended with a repeated dosing schedule). The RAAD effects of methylone are also similar to those reported in psilocybin trials for MDD and TRD and though not yet studied, may have "softer" effects. Given the similarities between methylone and MDMA and the high comorbidity between depression and PTSD, it is also important to highlight that these findings are similar in scope to the therapeutic effects seen in recent controlled clinical trials of MDMA for PTSD in conjunction with manualized psychotherapy, in which rapid and robust improvements were observed in severely ill, complex, and treatment-resistant patients [42].

It is notable that multiple patients reported improvements in relationships, including the start of a new romantic relationship, improved relationships (e.g., "enhanced connection," "cultivating better ways to relate,") with family members including children, and enhanced bonding with and "turning towards" the therapist. One patient also noted having significant anxiety about sharing emotional content (case 4), and found they were able to "come closer" to the therapist after methylone dosing, found the "courage to start" and then "words blast out" and he was able to begin processing. This increased sociability may be due to oxytocin [56], given the similar chemical structure between MDMA and methylone. While many of these outcomes are similar in nature and magnitude to those reported in both clinical trials and naturalistic settings with ketamine/esketamine, psilocybin and MDMA, there are critical aspects that are distinct between these compounds that warrant attention. Methylone is different in important ways that have potential to address known and expected barriers and limitations to broad implementation, scalability, and equitable access. Methylone's "softer" effects means that it may be safer and more appropriate for some patients who either have medical risks or contraindications (e.g., cardiovascular risks) or who may feel similar to one of the current participants that the other options have "too much thrust" and trigger anxiety. A benefit of methylone's less intense subjective effects is that they require less intensive medical monitoring, and can perhaps be safely administered to patients taking other serotonergic psychotropic medication which would circumvent the various challenges to weaning off. Based on the current case series, methylone also seems to have a durable effect, which addresses such concerns observed in, for example, ketamine treatment. The potential for a pharmacologic alternative that has "softer" effects and may require even slightly less intense infrastructure and resources to make scalable and accessible is urgently needed and warrant further investigation.

Strengths and Limitations

This case series provides encouraging evidence that methylone may have utility in the pharmacological treatment of MDD and TRD, with the potential for benefitting other stress- and trauma-related diseases including PTSD. These findings have important limitations. First, participants were treated clinically and data for this report were collected retrospectively from review of clinical records. There are no data regarding the semi-structured interviews and no further detailed information regarding symptom improvement that would provide a more fine-grained characterization of clinical benefit. A further limitation of the retrospective nature of this data is that we are unable to examine potential downstream effects of methylone and SSRIs that may interact in promoting clinical benefit. Second, dosing and follow-up were variable and there was no randomization, control, or blinding to treatment condition. It would be premature to draw conclusions regarding optimal dosage and duration of treatment from this preliminary report and well-controlled, randomized, and blinded trials will be important. Third, the sample is very small and lacks diversity. Much larger and more culturally diverse samples will provide information about generalizability and adaptation of methylone treatment to different populations [57,58].

Despite these limitations, these data from a complex patient

population constitutes the first clinical evidence for the efficacy of methylone in the treatment of MDD and TRD. A strength of this preliminary report is the complexity of the sample, which aids in generalizability and also speaks to potential issues with safety that address some current barriers to care with other currently available (ketamine) or soon-expected-to-be-approved (e.g., MDMA, psilocybin) interventions. Prospective well-controlled studies in larger and more diverse samples will be required to clarify the benefits and side effects of methylone and to optimize the dosing and strategies.

Methylone has not received the same cultural or clinical attention as MDMA, perhaps due to its milder psychopharmacological effects (e.g., stimulant, euphoric, empathogenic effects). However, these "softer" effects may be helpful for some patients who are not appropriate for treatment with the more intense acute psychological and physiological effects of MDMA. If future research supports the conclusion that methylone can produce rapid-acting and robust symptom improvement in MDD and TRD, it may prove to be an important and urgently needed addition to our pharmacological toolbox.

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